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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/995,636	11/29/2001	Leif Roge Lund	LUND-1A	3212

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EXAMINER	
WEBER, JON P	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 04/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/995,636	LUND ET AL.	
	Examiner	Art Unit	
	Jon P Weber, Ph.D.	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *5,9,27 and 34-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6-8, 10-25 and 28-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20011129*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Status of the Claims

Claims 1-39 have been presented for examination.

Election/Restrictions

Applicant's election **with** traverse of group I, claims 1-3, 12-22 and 28-30 in Paper filed 25 November 2003 is acknowledged. The traversal is on the ground(s) that Groups II and III are subsets of Group I, and Groups I and II were searched in the parent application. It is also argued that Group I is a subset of Group IV. This is found partially persuasive. The restriction between Groups I and II is withdrawn. However, Group III is drawn to a distinctly different invention, an inhibitor with the properties of inhibiting two classes of protease, whereas the first set of claims is drawn to a mixture of two inhibitors, one for each class of protease. It would require separate search and consideration of claims drawn to a single compound with the combined properties of two separate compounds. The claims of Group IV are so poorly characterized that a meaningful search could not be performed.

The requirement is still deemed proper and is therefore made FINAL. The restriction of Group V was **not** traversed.

Claims 5, 9, 27 and 34-39 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement. It is suggested that the non-elected claims be canceled in response to this Office action to expedite prosecution. Claims 1-4, 6-8, 10-25 and 28-33 remain to be considered on the merits.

Specification

The disclosure is objected to because of the following informalities:

There are numbers of misspellings such as "makroglobulin" and "phenanthrolene".

At pages 25-26 (and elsewhere) series of inhibitors identified such as "GI nnnnnn" and others such as Galardin, Zincov, batimastat and marimastat, are set forth which are clearly trademarks. The relationship between a trademark and the product it identifies is sometimes indefinite, uncertain and arbitrary. The formula or characteristics of the product may change from time to time and yet it may continue to be sold under the same trademark. In patent specifications, every element or ingredient of the product should be set forth in positive, exact, intelligible language, so that there will be no uncertainty as to what is meant. Arbitrary trademarks, which are liable to mean different things at the pleasure of manufacturers, do not constitute such language. Ex Parte Kattwinkle, 12 USPQ 11 (Bd. Apps. 1931). Generally, a trademarked material is described in generic terms at the first instance and is recited with ALL-CAPS throughout.

Appropriate correction is required.

Claim Objections

Claims 20, 23 and 24 are objected to because of the following informalities:

Claim 20 recites "neopiasms" which is a misspelling.

Claim 23 recites "makroglobin" which is a misspelling.

Claim 24 recites "phenanthrolene" which is a misspelling.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-8, 10-25 and 28-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite the negative limitations "the invasive remodeling not comprising contraction of tissue or corneal ulceration". The specification disclosure including the original claims has been carefully considered. No support for this new limitation can be found either expressly or implicitly. That is, there is no evidence that the subset of the genus of invasive remodeling not including these two species was ever contemplated or suggested; there is no explicit or implicit disclosure of either of these two species of invasive remodeling. This is a **new matter** rejection. It can be overcome by deletion of the new matter, or other appropriate action, such as providing evidence that the limitation is not new matter.

It is noted that the addition of these new limitations was made to overcome the objections under novelty and inventive step set forth in the written opinion of the EPO-IPEA. Cancellation of the negative limitations in response to this rejection would necessarily require addition of a rejection of the claims under 102 and/or 103 over the references cited in the written opinion, Khaw et al. (WO 9524921) and Schultz et al. (1992).

Claims 1-4, 6-8, 10-25 and 28-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The present claims are directed to "preventing or arresting invasive tissue remodeling in a mammal". The specification is not commensurate in scope with these claims because preventing or arresting invasive remodeling with a combination of serine protease and metalloprotease inhibitors is not taught in the specification. The specification is consistent with a reduction or inhibition of invasive remodeling, but not its "prevention or arrest".

Claims drawn to "prevention" or "arrest" bear a strong burden of proof. Prevention requires that the medical event does not happen in response to a challenge. Arrest requires that that a medical event in progress ceases completely in response to treatment. The instant specification provides several experimental evidences of the efficacy of the combined inhibitor treatment.

In example 6, normal $plg^{+/+}$ mice were treated with the combined regimen of aprotinin and tranexamic acid (plasmin inhibitors), and Galardin (metalloprotease inhibitor) in a wound-healing model. The results shown in figures 11-12 and the discussion at page 69 first full paragraph clearly indicate that systemic treatment with the two inhibitors reduced the invasive remodeling associated with wound healing but did not completely inhibit it as in the case of $plg^{-/-}$ mice and metalloprotease inhibitor experiment.

In example 7, normal $plg^{+/+}$ mice were treated with the combined regimen of aprotinin, tranexamic acid and Galardin in an embryo implantation model. The production of offspring was unaffected with the conclusion that the combined treatment does not lead to abolition of embryo implantation.

In example 8, normal $plg^{+/+}$ mice were treated with the combined regimen of aprotinin, tranexamic acid and Galardin in a Lewis Lung Tumor model. The results shown in figures 14-15 and discussed at page 73 demonstrate that tumor size and growth was inhibited but not prevented or arrested. A smaller reduction in tumor growth was obtained in example 9 with a human breast cancer xenograft.

Accordingly, the disclosure is consistent with reduction in or inhibition of invasive tissue remodeling by administration of a combination of inhibitors, not its prevention or arrest and clearly cannot be used as a means of contraception. It is interesting to note that: 1) in all of the combined therapies tested, two potent plasmin inhibitors were combined with a potent metalloprotease inhibitor, and 2) only these three potent inhibitors were tested for efficacy in the claimed method.

Claims 1-4, 6-8, 10-25 and 28-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for aprotinin and/or tranexamic acid in combination with Galardin, does not reasonably provide enablement for any plasmin inhibitor in combination with any metalloprotease inhibitor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

With respect to the adequacy of disclosure that a claimed genus possesses an asserted utility, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if it would be deemed likely by one skilled in the art, in view of contemporary knowledge in the art, that the claimed genus would possess the asserted utility. In re Oppenauer, 31 CCPA 1248, 143 F.2d 974, 62 USPQ 297; In re Cavallito et al., 48 CCPA 711, 282F.2d 357, 127 USPQ 202. For both adequate disclosure and/or enablement requires representative examples which provide reasonable assurance to one skilled in the art that the compounds falling within the scope of a claim possess the alleged utility and additionally demonstrate that applicant had possession of the full scope of the claimed invention. See In re Riat et al. CCPA 1964 327 F2d 685, 140 USPQ 471; In re Barr et al. CCPA 1971 444 F2d 349, 151 USPQ 724, for enablement and for disclosure see Court of Appeals for the Federal Circuit decision, The Regents of the University of California v. Eli Lilly and Company which can be found at the Federal Circuit web site, www.fedcir.gov as file 96-1175.

Claims drawn to pharmaceuticals and methods of treatment generally require supporting data because of the unpredictability in biological responses to therapeutic treatments. For the efficacy of a drug treatment *in vivo* faces unfavorable obstacles not present in *in vitro* models. As such, in vivo utility necessarily involves unpredictability with respect to physiological activity of an asserted process in humans. See discussion in Ex parte Kranz, 19 USPQ 2d 1216, 1218-1219 (6/90). For examples, drug delivery to the target area must survive the acidic environment of the stomach if administered orally. Additionally, the delivery of the drug across necessary cell surfaces in amounts needed to be efficacious, but not lethal to the subject, necessitates sensitive testing in order to adequately determine the proper human dosage.

The presently claimed invention encompasses a plethora of possible compounds of diverse structure and type for each class of inhibitor, and the use thereof as a pharmaceutical for treating a wide variety of invasive remodeling conditions. The lack of an adequate number of representative examples and the art-recognized unpredictability with respect to the effects on bioactivity preclude the making and use of compounds within the scope of the presently claimed invention by the skilled artisan without undue experimentation. The sole examples of combinations of inhibitors disclosed to have a synergistic effect have been discussed *supra*. While other inhibitors are alleged to be effective in the claimed process, synergism is inherently an unpredictable result. The vast number of possible combinations of inhibitors of each type, which could be combined to obtain the result of inhibiting invasive remodeling, is staggering. No possible reason is proposed why other appropriate combinations of inhibitors would be expected to obtain a synergistic result with any of the models. Issues of amounts, means of administration and efficacy have been adequately addressed for the scope of compounds envisaged. Some of the inhibitors listed in the claims are such weak inhibitors, e.g., EDTA, that it is doubtful that a therapeutically effect dose could be achieved.

Further to argue that one can make material embodiments of the invention and then test for those that work in the manner disclosed or that the instant claims only encompass the working embodiments would be judicially unsound. Unless one has a **reasonable expectation** that any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed or the instant specification provides sufficient guidance to permit one to identify those embodiments which are **more likely to work that not** without actually making and testing them then the instant application does not support the breadth of the

claims. In the instant case it is highly improbable that any combination of these inhibitor types will more likely than not perform in the synergistic manner disclosed and the instant specification does not provide the guidance needed to predictably select inhibitors from these two classes with any reasonable expectation that the resulting mixture will function as a synergistic inhibitor of invasive tissue remodeling.

Accordingly, the claims are not commensurate in scope with the enabling disclosure.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22-25 and 30-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 recites "for use in contraception" which lacks clear antecedent basis.

Claims 23 and 24 both recite "alpha-2-macroglobulin" as an inhibitor. It is not clear how the same compound can inhibit both classes belonging to vastly different classes of enzyme.

Claim 24 recites a series of inhibitors identified such as "GI nnnnnn" and others such as Galardin, Zincov, batimastat and marimastat, which are clearly trademarks.

"To describe physical or other properties of material by mere use of **trademark** is objectionable since it has tendency to make trademark descriptive of product rather than leaving trademark to serve its traditional purpose which is to identify product's source of origin". The issue involved the use of the Trademark **Hypalon** in the claims which Appellants have argued to be within the guidelines of M.P.E.P. 608.01 (v) if the meaning of the trademark is well known and satisfactorily defined in the literature. Copies of articles were submitted. No rejection was made based on first paragraph of 35 USC 112 which was correct but the rejection was on second paragraph which was considered to be correct by the board. "A patent applicant has an obligation that is imposed by 35 USC 112, second paragraph, to employ claim terminology which is definitive of what the public is not free to use, and use of a trademark in the manner employed by appellant has resulted in claims

which fail to meet this obligation in our opinion.: see **Ex parte Simpson and Roberts** 218 USPQ 1020.

Claim 24 recites "Ileu" which is not standard nomenclature.

Claim 25 recites "TIMP" which is not a standard abbreviation and should be spelled out at the first instance.

In claims 30-31, the phrase "such as" and the parentheses renders the claims indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6-8, 10-25 and 28-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Powers et al. (US 4,845,242), Powers et al. (US 5,514,694), Heath, Jr. et al. (US 5,441,984), Morphy et al. (US 5,714,491) and Morphy et al. (EP 648,205).

Powers et al. (US 4,845,242) and Powers et al. (US 5,514,694) disclose inhibitors of various serine and cysteine proteases that can be used to inhibit and treat tumor invasiveness and tissue remodeling mediated by serine proteases (col. 2).

Heath, Jr. et al. (US 5,441,984) disclose urea, thiourea and guanidine derivative inhibitors of collagenases and stromelysins to inhibit diabetic complications arising from alterations in invasive tissue remodeling (column 19-20).

Morphy et al. (US 5,714,491) and Morphy et al. (EP 648,205) teach peptidyl inhibitors of metalloproteases such as collagenase, gelatinase and stromelysin to control the invasive tissue remodeling associated with various diseases such as tumor metastasis.

These reference teachings or the equivalent acknowledgements would themselves support a *prima facie* case of obviousness since it has long been held obvious to combine two known materials for their known function, see *In re Kerhoven*, 626 F.2d 846, 205 USPQ 1069 (CCPA 1980); *In re Pinten*, 459 F.2d 1053, 173 USPQ 801 (CCPA 1972); *In re Lindner* 457 F.2d 506, 173 USPQ 356 (CCPA 1972); *In re Susi* 440 F.2d 442, 169 USPQ (CCPA 1971); *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1986)Id.

In the present case, however, there is additional evidence in the form of prior art disclosures which would have specifically motivated one of ordinary skill to make the claimed combination, with the expectation of accomplishing several highly desirable results."; *see Ex parte The NutraSeeet Co.* 19 USPQ2d 1586-90. Furthermore, the evidence of synergism disclosed is not commensurate in scope with the claims.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine a serine protease inhibitor with a metalloprotease inhibitor each known separately to inhibit tissue remodeling, with a reasonable likelihood that the combination of the two would similarly inhibit tissue remodeling.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon P Weber, Ph.D. whose telephone number is 571-272-0925. The examiner can normally be reached on daily, off 1st Fri, 9/5/4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon P Weber, Ph.D.
Primary Examiner
Art Unit 1651

JPW
30 March 2004